A

Synopsis

On the topic

"MULTIMORBIDITY IN STROKE IN INDIA (DATA FROM SPRINT INDIA TRIAL)"

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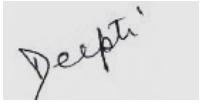
DECLARATION OF ORIGINAL WORK

I, the undersigned **Dr Deepti Arora** declare that the work embodied in this project work hereby, titled **"MULTIMORBIDITY IN STROKE IN INDIA (DATA FROM SPRINT INDIA TRIAL)"**, forms my contribution to the research work carried out under the guidance of **Dr Puja Gulati** is a result of my research work and has not been previously submitted to any other University for any other Degree/ Diploma to this or any other University.
Wherever reference has been made to previous works of others, it has been indicated as such and included in the bibliography.

I, hereby further declare that all information in this document has been obtained and presented per academic rules and ethical conduct.



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a. Introduction

The burden of Non-communicable diseases (NCD) is constantly rising. NCDs kill 41 million people each year, equivalent to 71% of all deaths globally; 85% of these deaths occur in low- and middle-income countries (LMICs).[1] Cardiovascular diseases (CVDs) remain the leading cause of disease burden in the world.[2] Prevalent cases of total CVD nearly doubled from 271 million in 1990 to 523 million in 2019.[2] CVDs principally Ischemic Heart Disease and Stroke, are the leading cause of global mortality and a major contributor to disability[3] followed by cancers, respiratory diseases and diabetes.[4]

Stroke is the second leading cause of death and the third leading cause of disability.[5, 6] According to the American Heart Association, stroke is defined as a neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause, including cerebral infarction, intracerebral haemorrhage, and subarachnoid haemorrhage. Ischemic stroke is an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction. Haemorrhagic stroke is a focal collection of blood within the parenchyma of the ventricular system that is not caused by trauma.[7] In 2016, the global prevalence rate (PR) of stroke was 80.1 million (74.1 to 86.3 million), with 84.4% of ischemic strokes.[5, 6] Prevalence is 18.3 million for ischemic stroke and 7.36 million for haemorrhagic stroke.[8] India stroke factsheet updated in 2012, the adjusted PR of stroke ranges from 84 to 262/100,000 in rural areas and 334 to 424/100,000 in urban areas.[9]

Multimorbidity: World Health Organization (WHO) defined the term "Multimorbidity" as the coexistence of two or more chronic conditions in the same individual.[10, 11] Relatively, comorbidity is defined as the medical condition that exists at the time of the diagnosis of the index disease.[12] Because of rising life expectancy and improvements in healthcare services, the world's population is ageing.[12] Physical and mental stress,[13] poor quality of life,[14] and adverse health outcomes[15] are all consequences of the rising prevalence of long-term non-communicable chronic diseases. Various additional factors, such as lack of education,[16] lack of medical services,[17] and lower socioeconomic status[16] have had negative effects on the population, especially in LMICs. This has resulted in increased hospital visits,[15, 18-20] polypharmacy,[15, 21] high prescription costs,[18-19] and rising mortality;[22-25] all these factors eventually lead to multimorbidity.

b. Research problem

Multimorbidity in Stroke in India (data from SPRINT India Trial)

c. Literature review

Many countries carried out the studies on the prevalence of multimorbidity like Japan 43%,[26] USA 77%,[27] Sweden 55%,[28] China 38%[29] and Netherlands 61-80%.[30] According to The WHO's Global Ageing and Adult Health (SAGE) wave 1 (2007-2010), the prevalence of non-communicable disease multimorbidity was 23% in the pooled sample of six countries.[31]

A systematic analysis of the prevalence of multimorbidity based on 70 community-based studies found a pooled prevalence of 31%.[32] Another systematic analysis of 21 studies reported a prevalence of 3.5 % to 98.5% in primary care and 13.1% to 71.8% in general populations.[33] The prevalence ranged from 4.5% to 83% from South Asia.[34]

Of the few existing studies on the prevalence of multimorbidity from LMICs, the prevalence is 53.8 % from Bangladesh.[35] 4%[36] from South Africa, 38%[37] from Ghana and 39.3%[38] from Brazil.

The prevalence of multimorbidity in India varies widely. The WHO's (SAGE) wave 1 study estimated the prevalence of multimorbidity in India as 24%.[31] Of the studies reporting multimorbidity in India, the lowest prevalence is 8.9%,[18] while the highest is 57.92%.[39] Multimorbidity affects nearly 1 in 10 urban South Asians.[22] The average number of aliments per person varied from 3.28[40] to 0.42.[18] INDEPTH (International Network for Demographic Evaluation of Populations and Their Health) found multimorbidity almost double in females (6.7% in women, 3.7% in men).[41] The prevalence of multimorbidity increase with age. Of the studies, one that reported age- and sex-adjusted prevalence of 28.3%, found that the highest prevalence was in the 70 and above age group (5.8% aged 18-29 years, 45% aged 70 years and above).[15] The other one, reported the adjusted prevalence and adjusted prevalence ratio of demographic and socio-economic factors of 9.4%, also found to be increasing with age (10% in those younger than 60 years and 37% in adults aged 60 years and above).[22]

Socioeconomic status (SES) is strongly associated with the prevalence of multimorbidity, regardless of whether SES is measured through education, occupation, behavioural factors or region (rural/urban). Those who are higher educated,[14-15, 42-43] tobacco users (chewed or smoked)[16, 31, 43] and alcohol consumers[22, 31, 43] are associated with a higher prevalence of multimorbidity. Multimorbidity is higher in both rural[18, 22, 35, 41] and urban[31] population. Furthermore, there is documentation of mortality associated with multimorbidity. CARRS Surveillance study (Cardiometabolic Risk Reduction in South Asia Surveillance Study), after adjusting for sociodemographic and health-related factors, reported that the mortality was 36% higher in those with single morbidity and 145% higher in those with multimorbidity.[22] A negative association between physical activity and multimorbidity has been observed.[14, 22, 31]. Multimorbidity was one and a half times higher than in obese individuals.[31] Multimorbidity is also positively associated with higher health care utilization, the number of hospital visits, hospitalizations and polypharmacy. In Orrisa, the number of hospital visits per person was 2.81 and the number of medicine users was 1.71 higher as compared to single morbidity.[15] The mean number of hospitalizations was 3 times higher in those who had multimorbidity as compared to the no morbidity.[16, 18]

Multimorbidity with stroke as the index condition has been studied in a few High-Income Countries. It is measured using the Charlson Comorbidity Index (CCI)[44], Elixhauser Index (EI),[45] and the count of diseases.[46] The number of diseases included ranged from 14[19-20] to 42.[23] The prevalence of multimorbidity in stroke ranges from 99.1%[19] to 42.8%[24] for ≥1 comorbidities. Hypertension, atrial fibrillation, diabetes mellitus, congestive heart failure, chronic obstructive pulmonary disease, and arthritis are the most common comorbidities recorded.[19-21, 23-24] The Danish study found that the proportion of people with stroke who had any comorbidity increased from 40.5% to 47.0% for ischaemic stroke and 32.0% to 44.7% for haemorrhagic stroke over the period of 18 years.[24] Stroke multimorbidity is associated with mortality both at short[25] and long[23-24, 47] term durations. Community studies from Spain[25] and USA[47] reported the patients with high CCI ≥ 2, having 68.4% and 72% greater odds of deaths at 6 months and at 1 year, respectively. The United Kingdom reported that the mortality risk doubles for those with ≥5 comorbidities compared to none over a period of 7 years.[23] Danish study reported that patients with stroke with very severe comorbidities had a 23.5% and 74.5% mortality risk at 30 days and 5 years, respectively, compared with 10.5% and 36.6% for patients with stroke with no comorbidities at baseline.[24]

d. Gaps in research

India's data is inadequate for the concepts and trends of multimorbidity in stroke. Though, studies were done in the individual states or cities, but not represent the population of India as a whole. The majority of data is disease-specific and fails to provide a comprehensive overview of the association of stroke with other diseases and outcomes. In India, to date, no study on multimorbidity have considered "stroke" as an index disease but has been studied as a group of long term chronic conditions. The impact of stroke multimorbidity on post-stroke quality of life,[11] particularly in terms of disability, self-management and medication non-adherence is not studied. Moreover, there is no literature on stroke multimorbidity in the young population. Polypharmacy also necessitated attention in areas where our expertise is still lacking.[11]

e. Need of the study

The need for study regarding multimorbidity in stroke in India is required to understand stroke relationship with multimorbidity and mortality. Large scale randomized control trials are required to develop a comprehensive analysis of multimorbidity in stroke for the cross-country comparison. There is no prospective evidence on the role of sociodemographic and lifestyle factors on the progression of stroke multimorbidity.

f. Objectives

This is the first attempt to map multimorbidity in stroke in the country. Our study's objectives are to determine the following for the SPRINT India Trial:

Primary objectives:

- to determine the prevalence of multimorbidity in stroke patients in the SPRINT cohort
- to understand the relationship between stroke multimorbidity and mortality

Secondary objectives:

- to assess the relationship between stroke and functional outcomes
- to determine a relation between the type of stroke (ischemic/haemorrhagic) and multimorbidity.

- to investigate the impact of sociodemographic and behavioural factors in stroke patients with multimorbidity
- to determine whether the multimorbidity in stroke is related to polypharmacy and increased hospital visits

g. Scope

The scope of the study is limited to 3400 stroke patients in 30 centres across India from the Sprint India Trial. Only the first-ever stroke patient's aged 18 years and above are part of the study. The stroke patients/family member who is literate and has mobile phones (preferably smartphone) are only included. As a result, India's illiterate population is excluded.

h. Delimitations of study

Since there is no guidance on conceptualizing multimorbidity in stroke patients, therefore simple count of chronic conditions (CCs) to quantify the burden of chronic conditions[48] is used. Further, only 12 chronic conditions in the count are considered, so likely to underestimate the prevalence of multimorbidity conditions in the Indian populations (39 in Scotland[21], 17 in Denmark[24], 19 in Spain[25] and 30 in Canada[20]). There are many prevalent chronic conditions like chronic obstructive pulmonary disease, depression, sleep and infectious diseases such as tuberculosis and HIV, which are not included. Many other sociodemographic aspects like marital status, insurance, income, financial burden are not explored. Moreover, the severity of multimorbidity is not studied.

i. Research questions

- What is the concept and pattern of multimorbidity in stroke in India?
- Which chronic conditions are most common in stroke multimorbidity?
- Which clusters of conditions have the worst prognosis in terms of outcome and mortality?
- What are the main sociodemographic factors associated with multimorbidity in stroke and to what degree do these factors synergise the risk of stroke?
- What are the most common short- and long-term complications in stroke multimorbidity?
- How do non-compliance in medication affect the outcome?
- What proportion of patients improves despite having multimorbidity?
- Does ischemic stroke have more multimorbidity or haemorrhagic?

- Do the intervention in the form of study material affect the outcome of the stroke?
- Is there any difference between men and women regarding multimorbidity in stroke?
- How do polypharmacy and the number of hospital visits affect multimorbidity in stroke?
- How are the results of the study going to help stroke patients in future?

j. Research Hypothesis

The study has the following hypothesis:

1. Multimorbidity in stroke has a positive association with health-related outcomes, namely mortality, vascular and non-vascular events in the SPRINT India Trial.
2. Multimorbidity in stroke exhibits a negative association between patient lifestyle factors and sociodemographic characteristics in the SPRINT India Trial.

k. Research design

1. Research methodology

The data for multimorbidity in stroke in India will be extracted from the **S**econdary **Pr**event**i**o**n** By Structured Semi-Interactive S**t**roke Prevention P**ac**kag**e** in INDIA (SPRINT INDIA). The study is an ongoing trial in 30 centres across India, in the Indian Clinical Stroke Trial Network (INSTRuCT network) initiated in 2017, funded by the Indian Council of Medical Research (ICMR), New Delhi, India.[49] The data will be collected both retrospectively (from April 2018) and prospectively (till March 2022). All the stroke patients in SPRINT India study will be screened and randomized using simple random sampling for our study's sample size. The prevalence will be calculated from the patients with multimorbidity. The patients with the presence of multimorbidity then will further associate with baseline characteristics and health outcomes.

Christian Medical College and Hospital Ludhiana (CMCL) Ethics Committee will approve the use of the data for this thesis. Approval will be taken from ICMR for the use of the data. The patient consent was not deemed necessary for this thesis as all of them were consented to while being part of the SPRINT India trial.

2. Area of study

The data is collected from 30 centres across India.[49]

3. Sample

The prevalence of multimorbidity was ranged from 75% to 94%.[19, 21] By considering the average proportion of 85%, the sample size was calculated to be n=3400 by using the formula $n = Z_{\alpha/2}\ 2 * P(1-P) / d^2$, where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (For our study the confidence level of 95%, α is 0.05 and the critical value is 1.96), p=85% is the proportion and d=1.2% is margin of error.

4. Technique

All the data is collected across the hospitals by a trained site coordinator appointed at each centre. Data is authenticated as it is collected from the medical records/OPD files/imaging/lab investigations and verified by the site neurologist.

5. Tools

A questionnaire "Multimorbidity in Stroke (data from SPRINT India Trial)" is prepared for extracting the data from the SPRINT India Trial.

6. Measurement and scaling:

All the demographic variables (age, gender, and region), socioeconomic variables (education status, occupation), multimorbidities (hypertension, diabetes, etc.) and outcome (disability, death) will be measured on a nominal scale. The variables like BMI, Blood pressure, Blood sugar etc. will be measured on an interval or ratio scale. The functional outcome mRS will be measured on an ordinal scale.

7. Data processing

All the data will be extracted from the electronic case record form of SPRINT India in excel.

8. Analysis and estimation

The data will be entered into a Microsoft Excel sheet. The categorical will be represented as Count (percentage) and continuous data will be represented in Mean±SD or Median (IQR). A Chi-square test will be used to find the association of the presence of multimorbidity with categorical baseline characteristics and health outcomes. Independent t-test or Mann Whitney U test will be used to find the association between continuous variables and the presence of multimorbidity. Logistic regression will be used to find the predictors for Multimorbidity and health outcomes. The P-value <0.05 will be considered significant. All statistical analysis will be performed using SPSS version 26.0.

9. Testing hypothesis

To test the population prevalence of multimorbidity in stroke patients and its correlation with health outcomes.

10. Expected outcomes

The expected primary outcomes are the measure of prevalence and outcome in the stroke patients with multimorbidity from SPRINT India data. The expected secondary outcomes are the type of stroke (evaluated at baseline using imaging CT/MRI), functional and neurological severity (assessed by mRS and NIHSS), sociodemographic factors (age, education, region, and residency) and behavioural factors (alcohol, tobacco, drug addiction, BMI, Blood pressure, medication adherence, physical activity) at 1 year.

11. Relevance of the expected results

Current stroke guidelines and healthcare services are not designed optimally for those with multimorbidity. The study will highlight several implications for future research on stroke multimorbidity in India, and its relationship with functional outcome,[23] mortality, sociodemographic and lifestyle factors. The results will aid in the redesign of stroke protocols for patients and the creation of a standardised approach to care and prevention at both the primary and secondary levels.

12. Timelines

Milestones of the study	Jun-21	Jul-21	Aug-21	Sep-21	Oct-21	Nov-21	Dec-21	Jan-22	Feb-22	Mar-22	Apr-22	May-22
Synopsis												
Research committee approval, CMCL												
Ethics committee approval, CMCL												
ICMR and sites' approval												
Recruitment												
Analysis												
Results												

13. Tentative chapter plan

S No.	Chapter
1	Introduction
2	Literature review
3	Research methodology
4	Results
5	Discussion
6	Strengths and limitations of the study
7	Recommendations for the future research

8	Conclusion
9	Abbreviations
10	Bibliography
11	Appendices

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